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Original Article

Design and Baseline Characteristics of an Observational Study in Japanese Patients with Hypertension: Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH)

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The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study is a nationwide, prospective, multicenter observational study that was designed to enroll hypertensive Japanese patients (>30,000 subjects). The patients in this study received treatment with open-label losartan, an angiotensin II receptor antagonist, for a maximum of 5 years. This report summarizes the study protocol and the baseline characteristics of the patients. Between June 2000 and May 2002, patients were screened in all 47 prefectures around Japan. Among the 31,515 patients screened, 31,048 patients were enrolled in this study and treated with losartan at a daily dose of 25–50 mg. These patients were 62.4±12.1 years old (mean±SD) and the mean clinic systolic/diastolic blood pressure (BP) values were 165.3±17.3/94.3±11.7 mmHg (mean±SD). The complications of hyperlipidemia, diabetes mellitus, cardiovascular disease, and cerebrovascular disease were also present in 38.5%, 13.1%, 8.0%, and 4.4% of patients, respectively. Regarding the World Health Organization classification, grade 2 hypertension was most frequent in this patient cohort. Nearly 10,000 patients agreed to perform home BP monitoring and report details regarding their lifestyles at baseline. Among the patients, 4.2% had white coat hypertension at the baseline. The J-HEALTH study is expected to provide valuable information about the significance of clinic and home BP control and home BP monitoring for the management of hypertension in Japanese patients. (*Hypertens Res* 2007; 30: 807–814)

***Key Words*: hypertension, losartan, blood pressure, cardiovascular disease, home blood pressure monitoring**

Introduction

Hypertension is one of the most important risk factors for the development of cerebrovascular disease, coronary heart disease, and renal disease (*1*). In Japan, management of hypertension is also one of the major public health issues, since there are approximately 30 million hypertensive patients (*2*).

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The goal of antihypertensive therapy is to reduce the incidence of hypertension-related events. Many large-scale clinical trials have already demonstrated the benefits of antihypertensive treatment with drug therapy (*3*, *4*). Based on these results, guidelines for the clinical management of hypertension such as "Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004)" and the recommendations of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) have been established and used in the daily management of hypertension (*5*, *6*). According to such guidelines, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are first-line agents for the treatment of hypertension, especially in hypertensive patients with diabetes.

Losartan potassium (losartan), a subtype 1 (AT1) selective angiotensin II (AII) receptor antagonist, has been widely prescribed worldwide. Several reports have suggested that losartan not only lowers the blood pressure (BP) values, but also has target organ protective effects. The Losartan Intervention for Endpoint Reduction (LIFE) study was a double-blind, prospective, parallel group trial that was designed to compare the effects of losartan with those of the β-blocker atenolol on cardiovascular morbidity and mortality in approximately 8,300 hypertensive patients with left ventricular hypertrophy. It demonstrated that losartan had a more favorable effect on cardiovascular events than atenolol (*7*). The Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study was a multinational, double-blind, randomized, and placebo-controlled trial that enrolled 1,513 patients with type 2 diabetes and nephropathy. It demonstrated a renoprotective effect of losartan (*8*).

Although studies conducted in Western countries have reported various beneficial effects of losartan therapy (*7–11*), the actual therapeutic benefit for Japanese patients has been unclear. Because the genetic and environmental background may differ between Japanese and Western patients (*12*, *13*), an investigation of the effects of losartan in Japanese hypertensive patients would be of value. Accordingly, the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study was initiated in 2000 as a large-scale observational study of losartan therapy.

Recently, the significance of home BP monitoring has been an important topic in the management of hypertension (*14–16*). Since large-scale analysis of home BP data has not been performed in Japan, direct evidence of the significance of home BP values for future cardiovascular events is still lacking (*17*). Accordingly, the J-HEALTH study was performed to investigate the long-term antihypertensive efficacy and safety of losartan, and the incidence of cardiovascular events and mortality in this population. The study also aimed to investigate whether home BP monitoring would be effective for use in routine antihypertensive treatment.

Table 1. Exclusion Criteria

- Pregnant or could become pregnant, or breast-feeding
- Severe hepatic or renal disease
- Diseases of poor prognosis; malignant neoplasm, performing hemodialysis, or virus infections such as HIV
- Taking the study drug prior to the registration
- Recent stroke or myocardial infarction within 1 month
- Other inappropriate conditions judged by each investigator

HIV, human immunodeficiency virus.

Methods

Objectives

This study was designed to enroll 30,000 patients with hypertension throughout Japan, and the patients were treated with losartan on an open-label basis at a daily dose at 25–50 mg with standard clinical management for a maximum of 5 years. The aims of this study were to investigate the efficacy and safety profile of losartan during actual clinical use in the 5-year post-marketing period, the incidence of cardiovascular events and mortality, the value of lifestyle modification as antihypertensive therapy, and the relationship between the clinic BP and the home BP values in Japanese hypertensive patients primarily treated with losartan.

Patients Recruitment

The eligible patients were men or women ≥20 years of age who were diagnosed as having hypertension by their physicians and had not taken any antihypertensive agents within the previous 1 month. Patients who had previously take losartan were excluded. The other exclusion criteria are shown in Table 1. Each patient was informed of the purpose and methods of the study, as well as the effects and possible risks of losartan therapy, the right to withdraw from the study at any time, and the measures for privacy protection before they were enrolled. Patients provided their verbal informed consent and then underwent a complete medical history review, physical examination, and laboratory evaluation.

Drug Treatment and Study Procedure

The patients were initially treated with losartan at a dose of 25–50 mg once daily (usually in the morning), which is the approved dosage in Japan. The dose was increased up to a dose of 100 mg once daily, if necessary. Addition of other antihypertensive agents was allowed from 3 months after the start of losartan treatment, if required. No restrictions were placed on the treatment of complications.

The enrolled patients were registered in a central study registry that included the following information at baseline:

Table 2. Patients' Characteristics at Baseline

	Men	Women	Total
Number of patients (*n* (%))	13,737	17,311	31,048
Age (years old)	60.0±12.0	64.3±11.8	62.4±12.1
SBP (mmHg)	164.4±17.0	165.9±17.4	165.3±17.3
DBP (mmHg)	96.2±11.6	92.8±11.6	94.3±11.7
BMI (kg/m^2)	24.3±3.3	23.9±3.8	24.1±3.6
Alcohol drinkers (*n* (%))	9,147 (66.6)	2,674 (15.4)	11,821 (38.1)
Current smokers (*n* (%))	6,085 (44.3)	1,664 (9.6)	7,749 (25.0)
Complications			
Hyperlipidemia (*n* (%))	4,935 (35.9)	7,005 (40.5)	11,940 (38.5)
Diabetes mellitus (*n* (%))	2,170 (15.8)	1,883 (10.9)	4,053 (13.1)
Cardiovascular disease (*n* (%))	1,097 (8.0)	1,400 (8.1)	2,497 (8.0)
Cerebrovascular disease (*n* (%))	616 (4.5)	745 (4.3)	1,361 (4.4)
Hepatic disease (*n* (%))	1,901 (13.8)	1,069 (6.2)	2,970 (9.6)
Renal disease (*n* (%))	509 (3.7)	496 (2.9)	1,005 (3.2)
ECG abnormality (*n* (%))	2,119 (15.4)	2,234 (12.9)	4,353 (14.0)
Concomitant drugs			
Lipid-lowering drugs (*n* (%))	2,632 (19.2)	5,033 (29.1)	7,665 (24.7)
Antidiabetics (*n* (%))	1,452 (10.6)	1,336 (7.7)	2,788 (9.0)
UA lowering drugs (*n* (%))	1,371 (10.0)	239 (1.4)	1,610 (5.2)
Aspirin or antiplatelets (*n* (%))	1,102 (8.0)	1,188 (6.9)	2,290 (7.4)

Mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; UA, uric acid.

demographic data, physical data (height and body weight), history of hypertension, and use of antihypertensive drugs; BP values and pulse rate; complications and medical history (renal disease, hepatic disease, cerebrovascular disease, coronary heart disease, endocrine/metabolic disease, and other diseases); laboratory test results (complete blood count, biochemistry tests, and urinalysis); lifestyle modification if performed (physical exercise, restriction of alcohol consumption or salt intake, ceasing smoking, weight loss, *etc.*); and electrocardiograph findings.

The following patient information was recorded in the worksheets and collected every year after the start of losartan-based antihypertensive treatment: adverse events, clinic BP values, pulse rate, heart rate, weight, daily dose of losartan, concomitant drugs, laboratory tests, and ECG (if performed).

The clinic BP was measured by the routine method at each institution. At each time of measurement, one clinic BP value was reported at the discretion of the physician. The clinic BP data measured at a maximum of 3 different visits prior to starting losartan therapy was used for calculation of the mean baseline clinic BP. After starting losartan therapy, the clinic BP value was measured every 3 months. The clinic BP data thus obtained were used for analysis of the clinic BP values during treatment.

The home BP was measured during the study by patients who voluntarily agreed to monitor their BP themselves. Home BP was measured with an electronic automated sphygmomanometer based on the cuff-oscillometric principal (HEM-740A; Omron Healthcare Co., Ltd., Kyoto, Japan). Patients who had already been using another device and insisted on continuing its use were permitted to do so. Patients were asked to measure the home BP at rest in the sitting position once every morning just after waking and urinating, and before medication. Home BP was measured once at one opportunity of measurement. If the patient measured home BP twice or more at one opportunity, the first measured value was reported. Home BP values obtained prior to the start of losartan therapy were used to calculate the mean baseline home BP. As a rule, morning home BP values measured each month, usually on the day of attending hospital, were used for analysis of the mean home BP value during treatment.

Standard laboratory tests (including ECG recording) were performed with the routine methods used at each institution, so standardization of measuring methods and reference values was not carried out. A maximum of 2 results of standard laboratory tests measured prior to losartan therapy were used to calculate the baseline values. After the start of losartan therapy, standard laboratory tests were performed every 6 months.

To assess the complications and the medical history, physicians judged the existence of diseases indicated in the registration form prior to the start of the study at their discretion.

In addition, the patients who were receiving drug treatment for hyperlipidemia or diabetes mellitus and met the definition of either disease indicated in the relevant guidelines were defined as having hyperlipidemia or diabetes.

All adverse events were recorded by the investigators and were classified as definitely related, possibly related, or defi-

Table 3. Distribution of Age and WHO Hypertension Grade, and Mean Blood Pressure at Baseline

	Men (N=12,698)		Women (N=16,250)		Total (N=28,948)	
	n (%)	SBP/DBP (mmHg)	n (%)	SBP/DBP (mmHg)	n (%)	SBP/DBP (mmHg)
Age (years old)						
20–39	556 (4.4)	160.1±16.0/102.2±11.3	261 (1.6)	163.5±16.7/101.9±10.6	817 (2.8)	161.2±16.3/102.1±11.1
40–59	5,518 (43.5)	163.5±16.7/100.1±10.4	5,494 (33.8)	167.1±18.2/97.9±10.5	11,012 (38.0)	165.3±17.6/99.0±10.5
60–79	6,029 (47.5)	165.5±17.0/92.9±11.1	8,963 (55.2)	165.3±16.8/90.6±10.7	14,992 (51.8)	165.4±16.9/91.5±10.9
≥80	595 (4.7)	165.4±18.9/87.0±11.5	1,532 (9.4)	166.0±18.4/85.7±12.1	2,127 (7.4)	165.9±18.5/86.0±12.0
BP classification						
Optimal to High-normal	349 (2.7)	130.2±8.4/77.0±8.2	499 (3.1)	130.3±8.3/75.7±8.6	848 (2.9)	130.3±8.3/76.2±8.5
Grade 1	3,282 (25.9)	149.9±6.7/89.1±7.5	4,349 (26.8)	150.6±6.1/86.7±8.1	7,631 (26.4)	150.3±6.4/87.7±7.9
Grade 2	6,027 (47.5)	164.2±8.6/95.9±8.5	7,619 (46.9)	165.9±7.2/92.8±9.1	13,646 (47.1)	165.2±7.9/94.1±8.9
Grade 3	3,040 (23.9)	184.3±15.7/106.6±12.0	3,783 (23.3)	188.3±14.5/102.0±12.6	6,823 (23.6)	186.5±15.2/104.1±12.5

Mean±SD. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

nitely unrelated to losartan, or as unknown. All losartan-related adverse events were pooled and classified as adverse drug reactions (ADRs).

Endpoint Evaluation

The primary endpoint of the study was a composite of cardiovascular events, including fatal or non-fatal stroke (new occurrence or recurrence of cerebral hemorrhage, cerebral infarction, or subarachnoid hemorrhage diagnosed on the basis of typical clinical symptoms persisting for more than 24 h and/or computerized tomography/magnetic resonance imaging findings), transient ischemic attack defined as a focal neurological deficit presumed to be vascular in origin persisting for less than 24 h, fatal or non-fatal myocardial infarction (new occurrence or recurrence) diagnosed on the basis of typical clinical symptoms, ECG changes and elevation of cardiac enzymes, or sudden cardiac death. In addition, the independent event classification committee reviewed adjudicated endpoint events on the basis of all available information documented in the case report form by the physicians.

Statistical Considerations

Determination of the Sample Size

When performing life-table analysis combined with the log-rank test, a 30% difference in the incidence of the primary endpoint (stroke, transient ischemic attack, acute myocardial infarction, or sudden cardiac death) was assumed between a subgroup of patients that represented 60% of the total population with higher BP and the remaining patients with lower BP. The incidence of stroke, myocardial infarction and sudden cardiac death in the Japanese population is 6.8/1,000 patient-years in men and 4.8/1,000 patient-years in women according to the Hisayama study (*18*), and the mean follow-up period for the J-HEALTH was 2.7 years. Thus, a total of 28,000 patients were required to detect the assumed between-group difference with a 90% power at α=0.05 (2-sided). Therefore, the target sample size was set at 30,000 patients.

Statistical Analysis

For the present interim analysis, variables were compared using the t-test, the χ^2 test, or analysis of variance (ANOVA). Results were expressed as the mean±SD, and differences were considered statistically significant at $p<0.05$.

Statistical analysis of the overall results was based on survival analysis. Subgroups were classified by the BP values at baseline or during treatment. Differences between subgroups were assessed by the log-rank test or the χ^2 test. Relationships between the endpoints and the BP values, as well as prognostic factors, were assessed by using the Cox proportional hazards model with adjustment for gender, age, alcohol drinker, current smoker, coexisting of cardiovascular disease, cerebrovascular disease, diabetes mellitus, and hyperlipidemia. For analysis of safety data, the number of ADRs, drug-related ADRs and other ADRs were calculated. For efficacy analysis, the antihypertensive effect of losartan with respect to both clinic BP and home BP values was assessed, and subgroup analyses were performed as described for the safety analysis. Comparison of safety and efficacy among the subgroups was performed with the χ^2 test, t-test, or ANOVA. Results were expressed as the mean±SD and a 2-sided $p<0.05$ was considered statistically significant. Statistical analysis was conducted with the SAS package (version 8.02; SAS Institute Inc., Cary, USA).

Organization

The organization and the members of the committees of the J-HEALTH study are given in the Appendix. These committees were responsible for performing the study or analyzing the data. The Monitoring Committee determined the validity of continuing the study based on the safety and effectiveness of losartan therapy from an ethical point of view. The Event Assessment Committee reviewed the events of cerebrovascular disease and coronary heart disease reported during the

Table 4. Lipid Profiles at Baseline

	Men (N=13,737)	Women (N=17,311)	Total (N=31,048)
Hyperlipidemia (n)	4,935	7,005	11,940
TC (mg/dL)	216.4±37.2	230.2±35.3	224.4±36.7
HDL-C (mg/dL)	51.5±15.5	59.2±16.3	56.0±16.4
TG (mg/dL)	214.2±142.9	159.9±96.3	182.8±121.3
Without hyperlipidemia (n)	8,802	10,306	19,108
TC (mg/dL)	189.3±29.0	199.5±29.6	194.7±29.8
HDL-C (mg/dL)	56.5±14.5	61.1±15.0	58.9±14.9
TG (mg/dL)	126.8±89.1	110.0±58.4	117.8±74.7

Mean±SD. TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides.

study. The Safety Assessment Committee assessed the causal relationship between the ADRs that are reported and the drugs that are administered during the study. The Medical Expert Advisory and Publication Committee was responsible for reviewing the results and writing the paper.

Results

Baseline Patients' Characteristics

Between June 2000 and December 2001, patients were screened in all 47 prefectures throughout Japan. The number of patients enrolled in this study per prefecture ranged from 165 in Okinawa to 2,667 in Tokyo. The distribution of patient enrollment was similar to the recent Japanese population statistics (*19*), and there were no major regional differences of BP values among the prefectures (data not shown).

A total of 31,515 patients were screened at 3,755 institutions by 4,149 investigators. Among them, 31,048 patients were enrolled in this study and 467 patients were excluded according to the exclusion criteria shown in Table 1 or withdrew their consent before actual enrollment. The baseline characteristics of the 31,048 enrolled patients (13,737 men [44.2%] and 17,311 women [55.8%]) are summarized in Table 2. The mean age of the patients was 62.4±12.1 years and the mean clinic systolic/diastolic BP (SBP/DBP) values were 165.3±17.3/94.3±11.7 mmHg.

Concomitant medications and complications are also listed in Table 2. All complications and ECG abnormality were diagnosed by the study investigators. The prevalences of hyperlipidemia, diabetes mellitus, cardiovascular disease, cerebrovascular disease, and ECG abnormality were 38.5%, 13.1%, 8.0%, 4.4%, and 14.0% respectively. Subjects taking anti-diabetic agents or lipid-lowering drugs were defined as having diabetes or hyperlipidemia, respectively.

Table 3 shows distributions of age groups and grade in the World Health Organization (WHO), and the mean BP values at baseline. Young patients (20–39 years) accounted for 2.8%, middle-aged patients (40–59 years) accounted for 38.0%, and elderly patients (60–79 years) made up 51.8% of the total patients. It is worth noting that there were 2,127 (7.4%) very elderly patients (≥80 years). The age distribution was generally similar between men and women. Then we analyzed the BP values of each age group. As shown in Table 3, the SBP values increased with age, but the difference was relatively small. On the other hand, the DBP values decreased markedly with age. Grade 2 hypertensive patients (based on the WHO classification) were most frequent in our cohort (n=13,646, 47.1%), while the numbers of grade 1 and 3 patients were almost equal (n=7,631, 26.4% *vs.* n=6,823, 23.6%, respectively).

The mean total cholesterol (TC) level of all patients was 209.6 mg/dL, while the mean TC levels of hyperlipidemic patients (n=11,940) and non-hyperlipidemic patients (n=19,108) were 224.4 mg/dL and 194.7 mg/dL, respectively. Details of the lipid profile are given in Table 4.

A total of 11,135 patients agreed to measure their BP values at home. Although data were limited at the time of enrollment (n=9,182), the scatter plot (Fig. 1) demonstrates the relationship between clinic BP and home BP for both the SBP and DBP values. The Pearson's correlation coefficients were 0.62 and 0.69, respectively. "White-coat hypertension" (WCHT) was defined by the following criteria: clinic SBP ≥140 or clinic DBP ≥90 mmHg and home SBP <135 and home DBP <85 mmHg. Based on these criteria, 4.2% of our patient cohort had so-called WCHT.

Discussion

The JSH 2004 have been published and updated periodically based on mainly Western epidemiological and clinical results (*5*). Although many large-scale investigational studies have been conducted worldwide to explore the management of hypertension (*3, 4*), it is difficult to determine which studies are best applicable to each individual case in clinical practice. Therefore, it is very important to clarify the characteristics, clinical effects, and safety profiles of various drugs in clinical practice. Many studies with Japanese hypertensives have been conducted, but these have usually employed small cohorts in rural areas. Practical information from large-scale investigational studies in clinical practice is limited in Japan (*20*). The J-HEALTH is a large-scale (30,000 patients)

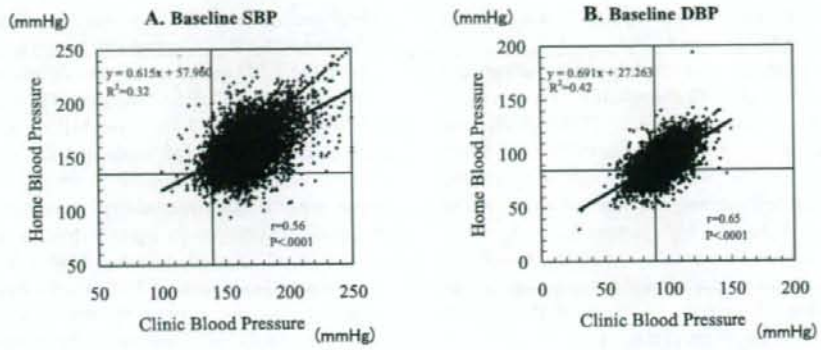

Fig. 1. *Scattered diagrams of clinic and home blood pressure at baseline (n=9,182). Each patient's clinic and home blood pressure was plotted for SBP (A) and DBP (B) with regression equations. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

nationwide multicenter observational study, which may provide us valuable epidemiological information on Japanese patients with hypertension.

The distribution of the hypertensive patients enrolled in the J-HEALTH study was similar to that of the recent Japanese population statistics (*19*). Thus, the patients in this study can be regarded as being representative of the overall Japanese population. Geographical differences in the prevalence of hypertension have previously been noted in Japan (*21*), with a higher incidence in the primarily rural northern part of Japan and a lower rate in the Western region (*5*). One of the reasons for the higher BP values in rural northern Japan is the high salt intake of the local population. However, no major regional differences of the mean clinic BP values were observed among the prefectures in the J-HEALTH study. This may reflect recent lifestyle changes and/or the widespread acceptance of antihypertensive therapy in Japan.

It is well known that vascular mortality increases with age, but the contribution of BP values to vascular mortality differs between age groups. The Prospective Studies Collaboration has published a meta-analysis of individual data for one million adults in 61 prospective observational studies of BP values and mortality (*22*). Although the proportional difference in the risk of vascular death is associated with an absolute difference in BP values, the proportional difference in vascular mortality is only about half as large at 80–89 years compared with that at 40–49 years. Therefore, the age of the subjects is an essential factor when analyzing study endpoints. The mean age of the J-HEALTH cohort is 62.4±12.1 years. On the other hand, the mean age was 67 years in the LIFE study (*7*). This age difference between randomized trials and actual clinical practice should be taken into consideration when applying the results of randomized trials.

The risks and benefits of treatment with antihypertensive agents are uncertain in patients older than 80 years (*23*). Gueyffier *et al.* suggested that antihypertensive treatment could prevent stroke, major cardiovascular events, and heart failure, but not cardiovascular death based on a meta-analysis of data from 1,670 patients aged 80 years or older (*24*). The Hisayama study suggested that the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) recommendations were not applicable to elderly Japanese persons over 80 years of age (*25*). Many very elderly hypertensive patients (≥80 years) were enrolled (595 men and 1,532 women) in the J-HEALTH study. Such a large number of elderly Japanese has not been studied before, so the results of the J-HEALTH study should be informative for this age group.

Of course, the BP is the most important characteristic of the patients in this study. The mean clinic SBP/DBP values of the J-HEALTH cohort were 165.3/94.3 mmHg. In contrast, the mean SBP/DBP values were 174.4/97.8 mmHg in the LIFE study. Based on their age and mean BP values, the J-HEALTH cohort is younger and has milder hypertension compared with the subjects of the LIFE study (*7*). Therefore, the J-HEALTH study may be able to assess the beneficial effects of ARB-based treatment for relatively low-risk hypertensive patients, who are the most common type encountered in clinical practice in Japan.

Not only the mean BP value itself, but also the grade of hypertension, is an important factor to be taken into consideration when evaluating a large-scale study. Grade 2 hypertension is the most frequent type in the J-HEALTH study population (47.1%). In their sub-analysis of the Hisayama study, Arima *et al.* excluded treated hypertensive patients and followed up 588 cardiovascular disease-free residents who were at least 60 years of age for about 30 years (from 1961 to 1993) to evaluate their cardiovascular risk. Among these patients, BP grade 1, 2, and 3 accounted for 27.2%, 18.6%, and 14.1%, respectively (they included normal BP and high normal BP subjects). Since the Hisayama study was an observational investigation of the general population, the hyperten-

sion stage distribution of the Hisayama population is different from that of the J-HEALTH cohort (*25*).

Complications represent another important background factor. The prevalences of ECG abnormality, cardiovascular disease, and cerebrovascular disease are 14.0%, 8.0%, and 4.4%, respectively, in the J-HEALTH cohort. These rates are lower than those in the LIFE study, again indicating that the J-HEALTH enrolled healthier subjects than the LIFE (*7*). The J-HEALTH cohort includes a high percentage of hyperlipidemic patients (38.5%). However, as shown in Table 4, the mean TC level of these hyperlipidemic patients is not extremely high, possibly because 24.7% of all the patients were taking lipid-lowering drugs (Table 3).

It has been emphasized that home BP values measured by ambulatory blood pressure (ABP) monitoring or self-measurement can be an important tool for the optimal management of hypertension with respect to cardiovascular risk (*26*). In the Pressioni Alteriose Monitorate e Loro Associazioni (PAMELA) study of 2,051 subjects who were representative of the general population, the clinic BP, home BP, and 24-h ABP values were measured. This study demonstrated that the risk of death increased more with a given increase in home BP or ABP than clinic BP values (*27*). Den Hond *et al*. investigated the diagnostic values of self-measured BP *vs*. ABP, and concluded that the specificity and sensitivity of ABP values for detecting WCHT were better than those of home BP values (*28*). While ABP values have better prognostic accuracy, the American Society of Hypertension Ad Hoc Panel recommends the use of home BP values for screening. Self-measurement of the BP is easy to repeat and is useful for patients to assess their own control (*29*). Hozawa *et al*. investigated the BP measured by home, ambulatory, and conventional methods in 1,174 Japanese subjects (150 with untreated hypertension, 399 with treated hypertension, and 625 normotensives). They also concluded that it was useful to measure the non-clinic BP values (*30*). We therefore determined the distribution and relation between clinic BP and home BP values at enrollment (Fig. 1).

WCHT is diagnosed by comparing the clinic BP and non-clinic BP values, and whether it causes target organ damage and cardiovascular events is one of the most important issues in the treatment of hypertension (*31*). The Ohasama study examined the prognostic significance of WCHT based on ABP monitoring, and concluded that the predictive power of the ABP values for subsequent mortality was stronger than that of the clinic BP values (*28*). The prevalence of WCHT is 4.2% in the J-HEALTH cohort, but the reported prevalence of WCHT in other studies varies widely because of differences in the definition of WCHT, method of BP measurement (self-measurement *vs*. ABP monitoring), and characteristics of the study population (untreated hypertension *vs*. treated hypertension). Masked hypertension (MHT) is also a topic of interest for antihypertensive therapy. The Self-Measurement of Blood Pressure at Home in the Elderly; Assessment and Follow-up (SHEAF) study demonstrated that about 9% of treated elderly patients had MHT and that the cardiovascular risk associated with MHT is significantly high (*32*).

A total of 9,182 patients measured their home BP values at the baseline in the J-HEALTH cohort. Therefore, we will use their data to identify WCHT and MHT and investigate the effect of home BP data on cardiovascular events. The home BP data obtained by self-measurement will display the time course effect of antihypertensive management and provide prognostic information for the hypertensive population.

The J-HEALTH study began in June 2000, and follow-up was completed in December 2005. The J-HEALTH study will clarify the long-term antihypertensive efficacy and safety of losartan-based therapy, and assess its preventive effect on hypertension-related diseases. It may provide new insights into therapeutic strategies for Japanese hypertensive patients.

Appendix

J-HEALTH Committees

Monitoring Committee: Takenori Yamaguchi (Chair), Tanenao Eto, Toshiharu Furukawa, Katsumi Yoshida.

Event Assessment Committee: Hiroaki Naritomi (Chair), Yoichiro Hashimoto, Uichi Ikeda, Mitsuaki Isobe, Toshio Kushiro, Ken Nagata, Kazuyuki Shimada, Takemori Yamawaki.

Safety Assessment Committee: Kendo Kiyosawa (Chair), Hiroshi Hirose, Sadayoshi Ito, Akinori Kasahara, Hiroshi Kawabe, Genjiro Kimura, Hirofumi Makino, Mitsuhiko Moriyama, Ikuo Saito, Hiromichi Suzuki, Eiji Tanaka.

Medical Expert Advisory and Publication Committee: Hiroaki Naritomi (Chair), Toshiro Fujita, Sadayoshi Ito, Toshio Ogihara, Kazuyuki Shimada, Kazuaki Shimamoto, Heizo Tanaka, Nobuo Yoshiike.

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Extremely Early Computed Tomography Signs in Hyperacute Ischemic Stroke as a Predictor of Parenchymal Hematoma

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Key Words
Acute stroke diagnosis · Computed tomography · Hemorrhagic transformation · Intracerebral hemorrhage · Ischemic stroke

Abstract
Background: In acute ischemic stroke, thrombolysis with intravenous recombinant tissue plasminogen activator is more effective when given within 90 min of onset compared to that given later than 90 min. However, the significance of early CT signs (ECTs) during such early periods has not yet been fully clarified. We investigated the usefulness of ECTs within 90 min for predicting parenchymal hematoma (PH) in patients without thrombolysis. ***Methods:*** We evaluated 212 consecutive patients with initial ischemic stroke in the anterior cerebral circulation who underwent the first CT within 6 h of onset. The patients were divided into 3 groups according to the interval from onset to CT: within 90 min (group A, n = 90), 91–180 min (group B, n = 76) and 181–360 min (group C, n = 46). Patients who had received thrombolytic therapy were excluded. ECTs were evaluated according to the Alberta Stroke Program Early CT Score (ASPECTS). The relationships between ECTs and the subsequent development of PH were compared among the groups. ***Results:*** In patients with ASPECTS values between 0 and 7, PH was developed more frequently in group A (35%) than in groups B (14%) or C (15%) (group A vs. B: p = 0.036, group A vs. C: p = 0.094). In group A, atrial fibrillation, elevated pretreatment blood pressure and ASPECTS ≤7 were independent predictors of PH. ***Conclusions:*** The manifestation of ECTs as represented by ASPECTS ≤7 within 90 min after stroke appears to indicate a high risk of PH.

Introduction

In hyperacute ischemic stroke, thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) was found to improve the 90-day functional outcome when given within 3 h of symptom onset in the National Institute of Neurological Disorders and Stroke (NINDS) trial [1]. On the other hand, the frequency of intracranial hemorrhage (ICH) was shown to increase significantly in stroke patients treated with thrombolysis [1–3]. Thus, the pretreatment predictors of ICH are currently one of the most important issues in clinical practice. At present, computed tomography (CT) is the most widely available and convenient technique for evaluating stroke, and the prediction of ICH using CT would be exceedingly valuable. The European Cooperative Acute Sroke Study (ECASS) investigators suggested that baseline early CT signs (ECTs), according to the so-called one third rule, could be predictive of ICH [2]. However, there was no reference to ECTs in the NINDS trial [1]. The subanalysis of NINDS data could not confirm the relationship between ECTs and ICH either, although they found such a ten-

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dency that symptomatic hemorrhages develop more commonly in patients whose ECTs extend over more than one third of the middle cerebral artery territory [4]. In addition, a recent meta-analysis of 6 major intravenous thrombolytic therapy trials suggests that the benefit of rt-PA is greater if started within 90 min compared to that later than 90 min [5]. However, the significance of ECTs in such very early periods has not yet been fully clarified.

Recently, a new scoring system was developed to better locate and semiquantify the early ischemic changes on CT: the Alberta Stroke Program Early CT Score (ASPECTS) [3]. This semiquantitative scoring method improved the interobserver agreement ratio [6] and facilitated the detection of earlier and more subtle changes [7]. We hypothesized that the time from onset to the appearance of ECTs would correlate with the severity of cerebral ischemia and the frequency of subsequent parenchymal hematoma (PH). We investigated the usefulness of ECT evaluation using ASPECTS within 90 min for predicting the risk of spontaneous PH in the following acute or subacute phase in patients without thrombolysis.

Patients and Methods

Patients

Among 1,679 patients with ischemic stroke admitted to the stroke care unit of the National Cardiovascular Center, Japan, between January 1998 and June 2005, we retrospectively evaluated 655 consecutive patients who underwent the first CT within 6 h after onset. We excluded patients with a history of symptomatic stroke or intracranial surgery. We also excluded patients with unclear onset including stroke at awakening and those with infarction limited to the posterior circulation alone. Thirty-five patients who had received thrombolysis (intravenous or intra-arterial) were also excluded. In Japan, the use of intravenous rt-PA for acute ischemic stroke was approved in October 2005, by which time the present study had been completed. Therefore, during the study period, thrombolytic therapy was performed only in patients who were enrolled in other clinical trials. Consequently, 212 consecutive patients with initial ischemic stroke in the anterior cerebral circulation were enrolled in this study. The 212 patients were divided into 3 groups according to the interval from onset to the first CT: within 90 min (group A, n = 90), 91–180 min (group B, n = 76) and 181–360 min (group C, n = 46). Anticoagulants and/or antiplatelet agents were administered to the patients in case the attending physicians considered these therapies were sufficiently safe and valuable.

CT Studies

All patients underwent noncontrast CT scans using an X-Vigor (Toshiba, Tokyo) on arrival. The scanning parameters were nonhelical, 120 kV, 170 mA, 10-mm collimation, matrix size of 512 × 512 and 2- or 3-second scan time. Routine photography was performed at window level and a width of 30 and 70–80 Hounsfield units (HU), respectively. Follow-up CTs were performed at 24 h and 7–14 days after stroke, as well as at the discretion of treating neurologists and reviewed in this study when performed within 14 days. All baseline CTs and follow-up CTs were retrospectively evaluated by 2 expert neurologists (S.O. and H.M.) with knowledge of the side of the affected hemisphere but blinded to treatment assignment, stroke severity or other clinical details. ECTs were scored according to ASPECTS [3, 6]. ASPECTS was assessed by scoring 10 regions (caudate nucleus, internal capsule, lentiform nucleus, insula and 6 cortical regions) systematically on the CT scan. A score of 1 was assigned for normal and 0 for a region showing ECTs. A normal CT scan has ASPECTS values of 10 points. Score 0 indicates diffuse ischemia throughout the territory of the middle cerebral artery. The ASPECTS study group suggested that baseline ASPECTS values in 2 categories (≤7 and >7) discriminated poor and good functional outcome, or high and low risk of ICH [3]. Therefore, we compared the incidence of ICH between a group with ASPECTS ≤7 and one with ASPECTS >7 in each period.

ECTs were defined as X-ray hypoattenuation, loss of the gray-white boundary or effacement of cortical sulci [3, 6]. ICH was classified as hemorrhagic infarction and PH; hemorrhagic infarction was defined as petechial infarction without space-occupying effect, and PH was defined as hemorrhage with mass effect. PH was subdivided into PH1, as blood clots in ≤30% of the infarcted area with some slight space-occupying effect, and PH2, as blood clots in >30% of the infarcted area with a substantial space-occupying effect, corresponding to ECASS II criteria [2]. In cases of disagreement in the findings, these 2 observers reviewed the CTs together and discussed the findings until a consensus was established.

Clinical Evaluation

Risk factors for ischemic stroke (i.e. age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation and smoking) were evaluated in all patients. According to the exclusion criteria of NINDS [1], we defined 'elevated pretreatment blood pressure' as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. Because the second analysis of NINDS showed that patients >75 years of age or with National Institutes of Health Stroke Scale (NIHSS) scores >20 were associated with poor outcome and high risk of ICH [9], we decided on the cutoff points of age >75 years and NIHSS score >20 on univariate analysis. The trial of ORG10172 in Acute Stroke Treatment criteria [10] were used to classify stroke subtypes.

Data Analysis

We determined the predictive value of ASPECTS referring to the findings of follow-up CT obtained at 24 h as a standard. ECTs were judged 'true positive' if a definite infarct was correctly located on the follow-up CT. If it was absent on the second CT, the reading was 'false positive'. The readings were judged 'true negative' if both baseline and follow-up CT did not reveal any infarcted changes. The readings were defined as 'false negative' if ECTs were not detected on the baseline CT and a definite infarct was visible on the follow-up CT. On the basis of these definitions, we assessed the predictive value in each of the 10 regions in each patient, then summed the results all together and calculated the sensitivity and specificity.

Table 1. Baseline characteristics of the 3 groups classified by time from stroke onset to initial CT

Variables	Group A 0–90 min)	Group B 91–180 min)	Group C 181–360 min)	p value
Patients	90	76	46	
Age, years	71 ± 11	70 ± 11	70 ± 12	0.783
Male	61 (68)	56 (74)	31 (67)	0.655
Hypertension	64 (71)	54 (71)	31 (67)	0.889
Diabetes mellitus	21 (23)	22 (29)	15 (33)	0.480
Hyperlipidemia	27 (30)	26 (34)	17 (37)	0.690
Atrial fibrillation	45 (50)	37 (49)	22 (48)	0.968
Smoking	25 (28)	23 (30)	12 (26)	0.588
Pretreatment, mm Hg				
Systolic blood pressure	162 ± 26	160 ± 26	171 ± 25	0.072
Diastolic blood pressure	87 ± 15	87 ± 13	90 ± 14	0.377
Elevated pretreatment blood pressure	20 (22)	12 (16)	9 (20)	0.578
NIHSS scores, median	12	9	6	0.097
1–5	20 (22)	24 (32)	21 (46)	
6–10	22 (24)	18 (24)	10 (22)	
11–15	14 (16)	7 (9)	5 (11)	
16–20	20 (22)	19 (25)	6 (13)	
>20	14 (16)	8 (11)	4 (9)	
ASPECTS, median	9	8	8	0.111
≤7	34 (37)	35 (46)	20 (44)	

Categorical values are expressed as numbers with percentages in parentheses, continuous variables as means ± SD. The χ^2 test was conducted for categorical variables, ANOVA for continuous variables and the Kruskal-Wallis test for scoring variables.

Statistical Analysis

Continuous data are expressed as means ± SD. For analysis of baseline characteristics, categorical variables were compared by χ^2 test, continuous variables by 1-way ANOVA and scoring variables by Kruskal-Wallis test. For univariate analysis of the predictors of PH, categorical variables were compared by χ^2 test, continuous variables by unpaired t test and scoring variables by Mann-Whitney U test. Multivariable analysis was undertaken using a logistic regression model. The results were considered significant at $p < 0.05$. Dr. SPSS II for Windows 11.0.1J was used for all calculations.

Results

Two hundred and twelve patients (148 men, 64 women) with ages ranging from 41 to 101 years (70 ± 11) were enrolled into this study. The stroke subtype was cardiogenic embolism in 118 patients, large-artery atherosclerosis in 29, small-vessel disease in 16 and other or unknown etiology in 49. As shown in table 1, the baseline characteristics were not significantly different between groups A, B and C.

ECTs were positive in 142 (67%) of the 212 patients. The predictive value for any ECTs with ASPECTS in each group was as follows: sensitivity 60% and specificity 95% in group A, sensitivity 79% and specificity 91% in group B, and sensitivity 75% and specificity 90% in group C. PH was observed in 25 (12%) of the 212 patients. PH1 occurred in 14 patients and PH2 in 11. There were no differences in baseline CT findings and clinical characteristics between PH1 and PH2. Antithrombotic agents were used in 188 patients (89%) within 2 weeks from onset; 143 patients (68%) were treated with intravenous heparin and 79 patients (37%) with antiplatelet agents. Among the 188 patients with antithrombotic therapy, only 15 (8%) developed PH. On the other hand, 10 (42%) of the 24 patients without antithrombotic therapy developed PH. Figure 1 shows the proportion of PH by ASPECTS category in each group. When the ASPECTS values were between 0 and 7, PH was developed in 12 (35%) of the 33 patients in group A, showing a significantly higher frequency as compared with group B (14%) or group C (15%) (group A vs. group B: $p = 0.036$, group A vs. group C: $p = 0.094$).

Table 2 details the univariate analysis of predictors of PH within 90 min. Atrial fibrillation, elevated pretreatment blood pressure, NIHSS score and ASPECTS ≤7

Table 2. Univariate analysis of PH predictors in cases of CT examination within 90 min

Variables	PH (16 patients)	no PH (74 patients)	p value	Odds ratio
Age	73 ± 11	70 ± 11	0.33	
>75 years	7 (44)	24 (32)	0.40	1.62 [0.54, 4.87]
Male	12 (75)	49 (66)	0.57	1.53 [0.45, 5.24]
Hypertension	14 (88)	50 (68)	0.14	3.36 [0.71, 15.98]
Diabetes mellitus	6 (38)	15 (20)	0.19	2.36 [0.74, 7.53]
Hyperlipidemia	5 (31)	22 (30)	1.00	1.07 [0.33, 2.65]
Smoking	8 (50)	39 (53)	1.00	0.90 [0.30, 2.65]
Atrial fibrillation	13 (81)	32 (43)	0.011	5.69 [1.49, 21.66]
Elevated pretreatment blood pressure	7 (44)	13 (18)	0.042	3.65 [1.15, 11.58]
NIHSS scores, median	16.5	10	0.006	
>20	4 (25)	10 (14)	0.26	2.13 [0.57, 7.93]
ASPECTS, median	5	9	<0.001	
≤7	12 (75)	21 (28)	0.001	7.36 [2.14, 25.33]

Categorical values are expressed as numbers with percentages in parentheses, continuous variables as means ± SD. Figures in square brackets are 95% confidence limits. Elevated pretreatment blood pressure is defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. Antiplatelet therapy includes aspirin, cilostazol, ticlopidine, argatroban and sodium ozagrel. Anticoagulant therapy includes heparin and warfarin.

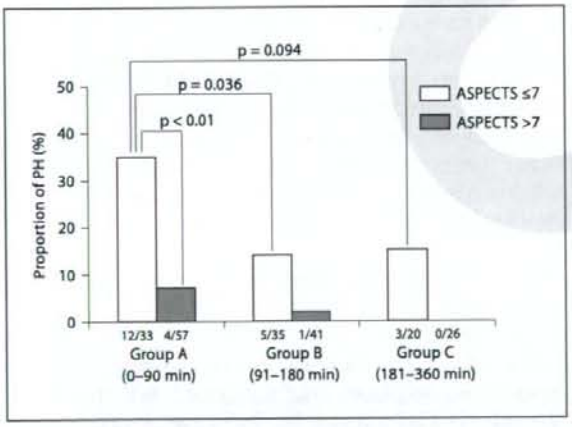

Fig. 1. Incidence of PH after ischemic stroke by categories of time from stroke onset to CT, comparing ASPECTS ≤7 with ASPECTS >7. Values are numbers of patients with PH divided by the total patients in each group (n/n).

were associated with PH. Multivariate logistic regression analysis for prediction of PH is presented in table 3. ASPECTS ≤7, elevated pretreatment blood pressure and atrial fibrillation were independent predictors of PH within 90 min of onset.

Table 3. Predictors of PH in cases of CT examination within 90 min: multivariable logistic regression analysis

	p value	OR	95% CI
NIHSS (per 1 score increase)	0.308	1.05	0.95–1.17
ASPECTS ≤7	0.013	6.14	1.47–25.66
Elevated pretreatment blood pressure	0.022	5.45	1.28–23.25
Atrial fibrillation	0.045	5.02	1.03–24.37

Elevated pretreatment blood pressure is defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. OR = Odds ratio; CI = confidence interval.

Discussion

We conducted the present study to evaluate the clinical significance of ECTs in the hyperacute phase of ischemic stroke and found that the manifestation of ECTs within 90 min after stroke indicates a high risk of subsequent PH. We evaluated PH as a type of ICH which may be more closely related with symptomatic deterioration than hemorrhagic infarction [11]. In our study, PH was observed in 12% of the patients. The frequency of PH was higher than that in ECASS II (3.1%) [2]. Okada et al. [12] reported that PH was found in 10% of 160 Japanese patients with acute

cerebral embolism. Because our study enrolled more patients with cardiogenic embolism than the ECASS II trial, the frequency of PH may become higher. Another explanation for the dissociation of PH frequency between our study and ECASS II is the racial difference in blood coagulation-fibrinolysis factors, such as fibrinogen and factor XII, between Japanese and Caucasians [13].

Several factors related to ECTs were reported to be important. CT density decreases linearly over time, describing the course of water uptake after ischemia [14]. The severity of perfusion impairment also correlates with the degree of CT density reduction [15]. In a recent study using single-photon emission CT, the time from onset to CT and residual cerebral blood flow were independent factors that contributed to the presence of ECTs [16]. Another study using positron emission tomography also shows that ECTs reflect the coupling of the severity of ischemia [17]. These findings suggest that the earlier the manifestation of ECTs, the severer the depth of brain ischemia. ECTs in the extremely early stage likely indicate severe ischemic brain damage associated with poor collaterals, leading to damage to the integrity of the blood-brain barrier [18]. Disruption of the blood-brain barrier contributes to the risk of ICH [19]. Our study showed that the sensitivity of ECTs was relatively low during the initial 90 min, however, the specificity was sufficiently high in each period. These findings were remarkably similar to the results of the study which assessed the significance of X-ray hypoattenuation at CT using the ECASS II population [20]. Careful detection of these subtle findings in the very early periods of ischemic stroke may facilitate the prediction of ICH.

The dichotomized score of ASPECTS 0–7 versus 8–10 was previously validated and shown to have prognostic value among patients treated with intravenous rt-PA for acute ischemic stroke within 3 h of onset [3, 6]. Recently, Dzialowski et al. [21] examined 800 patients within 6 h of stroke onset in the subanalysis of ECASS II and reported that ASPECTS ≤ 7 was a substantially increased risk of thrombolysis-related PH. These results are compatible with our study showing that in patients without thrombolysis, ASPECTS ≤ 7 was an independent predictor of PH, a sign of poor prognosis.

Several previous studies of intravenous rt-PA therapy suggested that ECTs were not associated with increased risk of ICH [4, 22]. These studies did not describe the interval between onset and CT, and the relationship between the ECT manifestation and the subsequent hemorrhagic transformation was not clarified. However, Demchuk et al. [22] concluded on the basis of such results that there was no evidence of treatment effect modification from the baseline ASPECTS value by thrombolysis. Data from animal models and human clinical trials have demonstrated that earlier stroke treatment is associated with better outcome [5, 23, 24]. There is a possibility that thrombolysis in the very early stage of ischemic stroke may diminish the disruption of the blood-brain barrier and reduce the risk of ICH.

The present study has several limitations. First, it was designed prior to the government approval of intravenous rt-PA in Japan. Therefore, we could not compare the neuroradiological and functional outcome between patients with thrombolysis and those without in spite of the fact that such a comparison may allow us to definitively define a subgroup of patients receiving benefit from thrombolysis. Second, we defined the ECTs according to ASPECTS criteria which include parenchymal hypoattenuation and brain swelling. There is increasing evidence that brain swelling without parenchymal hypoattenuation may be reversible [25]. On the other hand, brain swelling theoretically can represent early stages in a process that manifests finally as PH [26]. The actual relationship between brain swelling and PH remains unclear.

In conclusion, the manifestation of ECTs as represented by ASPECTS ≤ 7 within 90 min after stroke appears to indicate a high risk of parenchymal hemorrhage even when thrombolysis was not performed. Whether or not thrombolysis is indicated for such cases should be clarified in the future by a large-scale study.

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Review Article

Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands

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An international group of experts in pharmacokinetic modeling recommends a consensus nomenclature to describe *in vivo* molecular imaging of reversibly binding radioligands.
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Introduction

Imaging molecular targets such as receptors with positron emission tomography (PET) and single photon emission-computed tomography strongly relies on prior decades of research using *in vitro* radioligand techniques. These *in vitro* experiments are based on the equilibrium binding reaction between receptors R and free ligand F to form the bound ligand–receptor complex B, with reaction rate constants k_{on} and k_{off}.

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$$R + F \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} B \quad (1)$$

The term 'binding potential' was introduced for PET imaging and was also based on *in vitro* radioligand binding (Mintun *et al*, 1984). The concept was relatively simple and clarified the linear role of two parameters (receptor density and radioligand affinity) to determine the amount of radioligand uptake in brain. Specifically, Mintun *et al* (1984) defined binding potential as the ratio of B_{max} (receptor density) to K_D (radioligand equilibrium dissociation constant). Because affinity of ligand binding is the inverse of K_D, *BP* can be equivalently viewed as the product of B_{max} and affinity.

$$BP = \frac{B_{max}}{K_D} = B_{max} \times \frac{1}{K_D} = B_{max} \times \text{affinity} \quad (2)$$

The binding potential concept was embraced by the expanding field of radioligand imaging and often used as the primary outcome measure of experiments. Over several years, binding potential was defined in different ways and noted with varying abbreviations. The lack of consensus on nomenclature continues to cause significant confusion and often necessitates redundant explanations in manuscripts to clarify the specific terms used by the author. We propose a nomenclature that has broad support among experts in quantitation of *in vivo* radioligand binding.

Background

All *in vivo* studies of binding potential seek to measure a target receptor in terms of specific radioligand binding. Specific binding is defined as that associated with the target and distinct from radioligand which is free in solution or nonspecifically associated with other macromolecular components. Furthermore, the radioligand should be administered at tracer doses and thereby occupy a negligible (often defined as <5% to 10%) percentage of target sites. In this way, specific binding will reflect the entire population of target sites, without significantly perturbing the total number of available receptors. Finally, for the purpose of this presentation, we limit ourselves to radioligands that bind reversibly to a receptor, as the terms 'volume of distribution' and 'binding potential' are not useful for ligands that bind irreversibly. Note that by irreversible we mean a ligand that shows no clear evidence of dissociation over the time period of the PET or single photon emission-computed tomography study.

Cause of Discrepant Definitions

Binding potential quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration. The cause of the discrepant nomenclatures can be understood by the use of three distinct reference concentrations of the radioligand (Table 1). Because of these three reference concentrations, we recommend three abbreviations for binding potential measured *in vivo*.

BP_F refers to the ratio at equilibrium of the concentration of specifically bound radioligand in tissue to the concentration of free radioligand in tissue, which is assumed to equal the free concentration in plasma, if the ligand passes the blood–brain barrier only by diffusion (see discussion below).

BP_P refers to the ratio at equilibrium of specifically bound radioligand to that of total parent radioligand in plasma (i.e., free plus protein bound, excluding radioactive metabolites).

BP_{ND} refers to the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue. BP_{ND} is the typical measurement from reference tissue methods, as it compares the concentration of radioligand in receptor-rich to receptor-free regions.

With this nomenclature, *BP* without subscript refers to the 'true' *in vitro* measurement of B_{max}/K_D, and *BP* with subscripts refers to *in vivo* measurements that reflect, but typically do not equal, B_{max}/K_D. Specifically, these terms are proportional to the concentration of unoccupied or available receptor, B_{avail}. See below for discussion of *in vitro* versus *in vivo* measurements.

The motivation for this nomenclature is to remind the reader what factors are present in binding potential. The term BP_F reflects the ratio of specific binding to free radioligand at equilibrium. BP_P is not corrected for the fraction of ligand that is bound to plasma proteins (f_P), that is, BP_P equals the product of BP_F and f_P. BP_{ND} is not corrected for the free fraction of ligand in the nondisplaceable tissue compartment (f_{ND}), that is, BP_{ND} equals the product of BP_F and f_{ND}.

All three versions of binding potential have been used in different forms in the literature and have value depending on the particular application. For example, BP_{ND} does not require blood sampling and is relatively easy to implement. However, use of BP_{ND} as an outcome measure depends most heavily on the assumption that nondisplaceable uptake is independent of subject groups or treatment effects. BP_F and BP_P both require measurement of the arterial input function. While BP_F may be most

Table 1 Definitions of three *in vivo* binding potential values

Binding potential	*In vitro analog*	*Volume of distribution*	*Rate constants*	*Specific compared to:*	*Units*	*Plasma sample?*	*f_P?*
BP_F =	B_{avail}/K_D =	$(V_T - V_{ND})/f_P$ =	$\frac{K_1 k_3}{f_P k_2 k_4}$	Free plasma concentration	$mL \cdot cm^{-3}$	Yes	Yes
BP_P =	$f_P B_{avail}/K_D$ =	$V_T - V_{ND}$ =	$\frac{K_1 k_3}{k_2 k_4}$	Total plasma concentration	$mL \cdot cm^{-3}$	Yes	No
BP_{ND} =	$f_{ND} B_{avail}/K_D$ =	$(V_T - V_{ND})/V_{ND}$ =	$\frac{k_3}{k_4}$	Nondisplaceable uptake	Unitless	No	No

Rate constants are for the two-tissue compartment model. The two rightmost columns show whether each of the three binding potential values requires measurement of the concentration of radioligand in plasma (often arterial plasma) or the measurement of its plasma free fraction f_P. See Table 2 for definitions.

ideal from a theoretical view, BP_P may be more appropriate if the plasma free fraction is difficult to measure accurately or has a small range with no difference between groups, that is correcting for protein binding differences could simply add more variability to the data.

Volumes of Distribution

In clinical pharmacology, 'volume of distribution' typically refers to the volume of blood (or plasma) that would be required to account for the amount of drug in the entire body. For example, if the concentration of drug in plasma is $200\,ng \cdot mL^{-1}$ and 10 mg of drug are in the entire body, then its volume of distribution would be 50 L. That is, 50 L of plasma contains the same amount of drug as the entire body.

The field of *in vivo* imaging with radioligands adapted this concept in two ways. First, the target region was regarded as a particular organ (e.g., brain) rather than the entire body. Second, instead of referring to the amount of drug in the entire organ, the target was expressed as the amount of radioligand in a volume of tissue (i.e., a concentration). For example, if the concentration of a radiopharmaceutical at equilibrium is $100\,kBq \cdot cm^{-3}$ in striatum (C_T) and $5\,kBq \cdot mL^{-1}$ in plasma (C_P), then its volume of distribution (V_T) is $20\,mL \cdot cm^{-3}$. That is, 20 mL plasma would be required to account for the radioligand in just $1\,cm^3$ of brain. The units of this new 'volume of distribution' are not volume (mL) but a ratio of two volumes (mL and cm^{-3}). Furthermore, although $1\,cm^3 = 1\,mL$ by SI nomenclature (Taylor, 1995, Table 6, p. 8) and this 'volume of distribution' would appear to be strictly unitless, it is important to maintain the units. In summary, the volume of distribution used in most imaging studies is the ratio of the concentration of radioligand in a region of tissue to that in plasma. We express the volume of distribution in units of $mL \cdot cm^{-3}$ to clarify that it is a ratio of mL of reference fluid to a volume of tissue, where fluid volumes are measured in milliliter and physical volumes are measured in cubic centimeter from PET or single photon emission-computed tomography.

Tissue may contain radioligand that is specifically bound to receptors (S), nonspecifically bound (NS), or free in tissue water (F). Thus, the total concentration of radioligand in the tissue (C_T) can be expressed as follows:

$$C_T = C_S + C_{NS} + C_{FT} \quad (3)$$

Furthermore, nondisplaceable (ND) uptake is the sum of nonspecific (NS) and free ligand in tissue.

$$C_{ND} = C_{FT} + C_{NS} \quad (4)$$

The volume of distribution of these three components equals the ratio *at equilibrium* of each concentration to that of parent radioligand (C_P) in plasma, separated from radiometabolites.

$$V_T = \frac{C_T}{C_P} = V_{FT} + V_{NS} + V_S = V_{ND} + V_S \quad (5)$$

$$V_{NS} = \frac{C_{NS}}{C_P} \quad (6)$$

$$V_{ND} = \frac{C_{ND}}{C_P} \quad (7)$$

$$V_S = \frac{C_S}{C_P} \quad (8)$$

Free Fractions f_P and f_{ND}

The free fraction of drug or radioligand in plasma is the fraction of the ligand that is not bound to plasma proteins at equilibrium, i.e., that which is freely diffusible in plasma water. The plasma free fraction is referred to as f_P, and the concentration of free drug in plasma C_{FP} can be calculated as

$$C_{FP} = f_P C_P \quad (9)$$

The comparable term f_{ND} is the fraction of drug that is freely dissolved in tissue water. This tissue free fraction f_{ND} is expressed relative to the nondisplaceable compartment.

$$C_{FT} = f_{ND} C_{ND} \quad (10)$$

The parameter f_{ND} is defined with respect to the nondisplaceable compartment and is, thereby, usually assumed to be equal in receptor-rich and receptor-free regions, assuming that nonspecific binding (NS) is the same in both areas.

Relation of Binding Potential to Volumes of Distribution

An important corollary of Mintun's formulation is that binding potential equals a particular volume of distribution, namely, that of the specific (receptor bound) radioligand. The equivalence of these two concepts can be seen from the Michaelis–Menten equation describing *in vitro* receptor binding under equilibrium conditions.

$$B = \frac{B_{max} F}{K_D + F} \quad (11)$$

where B is the concentration of receptor bound ligand, B_{max} the density of receptors, F the concentration of free radioligand, and K_D is the dissociation constant. For low mass dose studies typical of radioligand imaging, $F \ll K_D$; thus, equation (11) reduces to

$$\frac{B}{F} = \frac{B_{max}}{K_D} = BP \quad (12)$$

Thus, at tracer doses, Mintun's original definition of binding potential (B_{max}/K_D) equals the equilibrium

ratio of specifically bound ligand (B) to its free concentration (F). *In vitro* radioligand binding contains only one compartment, and no distinction is appropriate for the free concentration in plasma compared with that in tissue. Conversion of the *in vitro* terms to *in vivo* imaging is as follows:

$$B = C_S \tag{13}$$

$$F = C_{FT} \tag{14}$$

$$\frac{B}{F} = \frac{C_S}{C_{FT}} = \frac{B_{avail}}{K_D} = BP_F \tag{15}$$

Equation (15) is valid if the ligand enters and leaves tissue by passive diffusion, so that at equilibrium the free concentration in plasma equals the free concentration in tissue, that is $C_{FP} = C_{FT}$.

Note that *in vitro* assays typically use homogenized tissue in which all receptors are available to bind to radioligand. In contrast, only a subset of these receptors (B_{avail}) are available *in vivo* to bind to radioligand, since some may be compartmentalized, in a low affinity state, or occupied by endogenous transmitter.

After the pattern of clinical pharmacology, the proposed nomenclature could have used only volumes of distribution and not binding potential. Instead, we elected to use portions of both nomenclatures. Binding potential was maintained because of widespread use in imaging and its important theoretical connection to *in vitro* receptor binding (equation (11)). As binding potential refers to specific binding, additional terms are necessary to describe nondisplaceable and total uptake of radioligand into tissue. We elected to use V_T for the distribution volume of total ligand uptake in tissue relative to total concentration of ligand in plasma, since most clinical pharmacology studies use this definition. V_{ND} is the distribution volume of nondisplaceable compartment relative to total concentration of ligand in plasma, where $V_{ND} = V_F + V_{NS}$.

Because specific binding equals $V_T - V_{ND}$,

$$BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}} = \frac{V_T}{V_{ND}} - 1 \tag{16}$$

The term V_T/V_{ND} is sometimes termed the 'distribution volume ratio' (DVR). BP_{ND} does not generally require arterial plasma measurements and, under typical assumptions, can be 'directly' calculated from only brain data using a variety of reference tissue methods (Gunn *et al*, 1997; Lammertsma and Hume, 1996; Logan *et al*, 1996). Nevertheless, BP_{ND} can be 'indirectly' calculated from volumes of distribution measured with arterial plasma concentrations of radioligand, as shown in equation (16).

BP refers to specific binding as a ratio to other concentrations (free in plasma, total in plasma, and nondisplaceable). In contrast V can be used for specific, nondisplaceable, or total uptake but is always a ratio to total radioligand concentration in plasma. Thus, when numerator and denominator are the same, this nomenclature has two redundant terms, that is $V_S = BP_F$. Nevertheless, we recommend this redundancy, because a single document may need terms for only V and another for only *BP*.

Units of Rate Constants

The standard one- and two-tissue compartment models used in kinetic studies are shown in Figure 1. By common practice, we recommend that the rate constant for transfer from arterial plasma to tissue (K_1) use upper case, whereas the remaining rate constants (k_2, k_3, and k_4) are lower case. The primary reason for this special distinction is to note that the units of K_1 are different from those of the other rate constants. K_1 commonly has units to reflect volume of blood (or plasma) per volume of tissue per minute, whereas the other transfer rate constants (k_2, k_3, and k_4) have units of min^{-1}. K_1 is often given in units of $mL \cdot mL^{-1} \cdot min^{-1}$, which refers to mL plasma per mL tissue per minute. However, mL is generally reserved for fluids, whereas cm^3 is used for solids (Taylor 1995, Section 8.2, p. 23). Thus, we elected units of K_1 to be $mL \cdot cm^{-3}$ to distinguish mL plasma from cm^3 tissue (Table 2).

The ratio of K_1 to the remaining rate constants will have units of $mL \cdot cm^{-3}$. As shown below, such ratios determine binding potentials and volumes of distribution, which therefore can also be considered to have units of $mL \cdot cm^{-3}$. The use of separate units for plasma (mL) and brain (cm^3) helps to clarify that the 'volumes' in volumes of distribution refer to the mL plasma required to account for ligand in $1\,cm^3$ tissue.

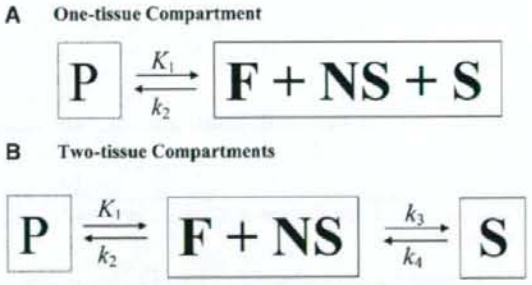

Figure 1 Common compartment models. (**A**) One-tissue compartment model. The tissue is considered to have just one compartment, that is the free and nonspecifically bound ligand cannot be kinetically distinguished from the specifically bound. This model is typically called 'two compartment' (for two 'boxes') in clinical pharmacology but 'one-tissue compartment' in radioligand imaging. (**B**) Two-tissue compartment model. Two of the compartments ('boxes') are located within the tissue: nondisplaceable, that is free plus nonspecific (F + NS) and specific (S). Input to the tissue derives from the plasma (P). This model is typically called 'three compartment' (for three 'boxes') in clinical pharmacology but 'two-tissue compartment' in radioligand imaging.

Relation of Compartmental Rate Constants to Binding Potential and Distribution Volume

An important concept of pharmacokinetics is that the ratio of compartmental rate constants equals selected equilibrium distribution volumes. The derivation of these relationships is included in many publications (see, e.g., Koeppe *et al*, 1991; Lassen, 1992). Using the current nomenclature, the resulting equations for *BP* are included in Table 1 in terms of volumes of distribution. For one- and two-tissue compartment models, volumes of distribution can be calculated from rate constants as follows.

One-tissue compartment model:

$$V_T = \frac{K_1}{k_2} \tag{17}$$

Two-tissue compartment model:

$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) \tag{18}$$

$$V_{ND} = \frac{K_1}{k_2} = \frac{f_P}{f_{ND}} \tag{19}$$

Equation (19) can be derived from equations (9) and (10) under the assumption that at equilibrium, if the ligand enters and leaves tissue by passive diffusion, the free concentration in plasma equals the free concentration in tissue, that is $C_{FP} = C_{FT}$. Note that strictly this is not the case, but rather the concentration at equilibrium in the aqueous phase of plasma is equal to the concentration in the aqueous phase of tissue. As the aqueous volume fractions in plasma and tissue differ, we should add these volume fraction terms to equation (19). However, we chose to leave equation (19) in this form, with the proviso that, strictly, f_P and f_{ND} are not dimensionless, but include the correction for aqueous volume fractions in plasma and tissue. Note that both these fractions are close to 1.0.

Relation of *In Vitro* Receptor Binding to Kinetic Parameters

The central concept of the *in vivo* binding potential is that it measures the ratio of the available receptor density to the equilibrium dissociation rate constant, both of which had been investigated in prior decades using *in vitro* techniques. Most investigators think that radioligand measurements of binding potential reflect B_{avail}/K_D, although the subtleties of the *in vivo* condition continue to be investigated actively. The *in vivo* rate constants have also been compared with *in vitro* rate binding constants. With the assumptions that the *in vivo* k_4 equals the *in vitro* k_{off} and that the free and nondisplaceable ligand are in rapid equilibrium, the relevant equations for the two-tissue compartment model are shown below.

$$\textit{In vitro} \qquad K_D = \frac{k_{off}}{k_{on}} \tag{20}$$

$$\textit{In vivo} \qquad k_3 = f_{ND} k_{on} B_{avail} \tag{21}$$

$$k_4 = k_{off} \tag{22}$$

If these *in vivo* equations for k_3 and k_4 are substituted in Table 1 (column of rate constants), they do mathematically confirm that $BP_F = B_{avail}/K_D$, under the assumption of passive diffusion of the radioligand across the blood–brain barrier. Nevertheless, several radioligand studies suggest that the *in vivo* k_4 is much smaller than the *in vitro* k_{off}, as stated in equation (22). That is, the *in vivo* rate of dissociation (k_4) is much slower than the *in vitro* rate (k_{off}). This phenomenon has been shown for several neuroreceptor ligands in which displacement of the radioligand occurs far more rapidly than could be attributed to the slow k_4 rate measured in typical baseline conditions of negligible receptor occupancy (Laruelle *et al*, 1994; Robertson *et al*, 1991). Despite this apparent discrepancy between k_4 and k_{off}, both k_3 (which posited as a function of three variables) and k_4 appear to be similarly decreased by a constant factor such that their ratio is proportional to the *in vivo* K_D, which sometimes approximates that found *in vitro*. The cause of this apparent proportional scaling in k_3 and k_4 is unknown but has been ascribed to radioligand rebinding in a relatively isolated compartment referred to as the synaptic barrier (Delforge *et al*, 1996; Votaw *et al*, 1993).

The total available receptor concentration (B_{avail}) can be measured *in vivo* if imaging is performed at multiple specific activities, that is by varying the occupancy of the receptor by the radioligand. Such studies may be useful to help elucidate the differences between *in vitro* and *in vivo* conditions.

In summary, most researchers think that BP_F reflects *in vivo* measurements of B_{avail} and K_D. Nevertheless, conditions for *in vivo* radioligand binding may differ in many ways from the controlled *in vitro* environment, including temperature, multiple compartments, receptor trafficking, phosphorylation state, and competition with endogenous neurotransmitter. Although the result of complex conditions, *in vivo* radioligand binding can sometimes monitor important parameters like competition with the endogenous transmitter (Laruelle, 2000).

Receptor Occupancy and Displacement

A wide variety of imaging studies are aimed at measuring changes in occupancy of receptors owing to exogenous drugs or endogenous neurotransmitters.